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CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS
QUICK REFERENCE GUIDE

Contents

Introduction

In 1998 the Spanish Society of Rheumatology (SER) decided to develop a Clinical Practice Guideline (CPG) to help physicians make decisions about the diagnosis and treatment of patients with rheumatoid arthritis (RA). This initiative of the SER was in response to a phenomenon frequently seen in clinical practice: the large variability in the use of diagnostic, therapeutic and rehabilitative procedures. The enormous amount of information produced as a result of a growing number of studies, their variable methodological quality, and the complexity of comparing the results of different studies constitute a major obstacle for clinicians in keeping up to date on important knowledge in their field. This situation prompted the idea of producing a CPG for the management of RA (GUIPCAR), which was undertaken by the Health Services Research Unit (UISS) of the Carlos III Health Institute. This project took 2 years to complete. During this time, the UISS became a private company with the name of Advanced Research Techniques in the Health Services (TAISS).

RA is a systemic disease, of unknown etiology, which is characterized by chronic inflammation of the diarthrodial joints and is usually associated with severe morbidity. It is estimated to affect some 200,000 persons in Spain, with 20,000 new cases occurring each year. The quality of life is reduced in most patients, who usually experience changes in functional capacity, with work disability and increased mortality.

RA also produces an enormous social cost. It has been estimated that the annual cost of this disease in Spain exceeds 200 billion pesetas (US$1.04 million), of which 65 billion pesetas ($338.5 million) are devoted to health expenditures.

There is evidence of large variability in the management of RA in Spain; this variability depends not only on patient or disease characteristics, but also on characteristics of the hospital, department, or physician providing patient care. For example, the mean number of patient visits in one center may be double that of another, after adjusting for disease severity and functional class. Even more variability has been seen in other areas, such as the use of diagnostic tests or management of treatment. These facts may suggest that some diagnostic or therapeutic procedures are of uncertain value while other, appropriate procedures may be underused.

Objectives

The main objective of this guideline is to develop high quality criteria for the treatment of RA and to reduce the variability that is not dependent on patient characteristics.

Contents and Methodology

This guideline describes the diagnostic and management strategies that an expert panel considered appropriate for the evaluation and treatment of patients with RA. It focuses on RA in adults (excluding juvenile RA) and includes diagnosis, evaluation, prognosis, and treatments such as drugs, rehabilitation, and surgery. It does not cover other treatments such as acupuncture, and only briefly treats extra-articular complications of RA such as amyloidosis, anemia, or Sjögren's syndrome.

The guideline recommendations can be applied in both the hospital and outpatient setting except for some, such as the guidelines for surgery, which obviously can only be performed in specialized centers. This guideline is intended for rheumatologists and recommends that the diagnosis, monitoring, and treatment of RA be carried out by physicians who are trained to identify patients in the early phases of disease, to evaluate the disease stage, to suggest appropriate treatment for each stage in the evolution of the disease, and to measure the response to treatment.

The recommendations for treatment with disease-modifying anti-rheumatic drugs (DMARDs) in this guideline are based on a synthesis of the best available scientific evidence after making a systematic review of the literature. The rest of the recommendations or considerations are based on scientific evidence obtained without a systematic literature review, or on the opinions of the expert panel.

Using the Quick Reference Guide

This quick reference guide describes the most important recommendations contained in the guideline. The recommendations are presented in this summary in an abbreviated form. Readers should refer to the text of the guideline to see the complete recommendation, discussion, levels of evidence, and bibliographic references. This quick reference guide includes a simplified algorithm. The algorithms included at the end of the guideline allow the user to follow a logical decision-making process in managing the patient.

DIAGNOSING RHEUMATOID ARTHRITIS

RA should be suspected in patients over 16 years of age who have joint inflammation or

effusion of more than 6 weeks duration in three or more joints, preferably of the hands and feet. To date, the only universally accepted and used diagnostic criteria for RA are those proposed by the American College of Rheumatology (ACR) for classification of the disease.

According to the ACR, the diagnosis of RA requires confirmation of at least four of the following criteria:

1. Morning stiffness lasting at least one hour before maximal improvement, for at least 6 consecutive weeks.
2. Soft tissue swelling or effusion, observed by a physician, in at least three of the following joint areas (right or left): proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, knee, ankle, or metatarsophalangeal (MTP) joints, for at least 6 consecutive weeks.
3. Swelling or effusion, observed by a physician, in the proximal interphalangeal, metacarpophalangeal, or wrist joints, for at least 6 consecutive weeks.
4. Symmetrical (right and left sides) swelling or fluid in the joints mentioned in point 2, observed by a physician, for at least 6 consecutive weeks.
5. Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions, observed by a physician.
6. Demonstration of serum rheumatoid factor (RF) detected by any method that has been positive in less than 5% of control subjects.
7. Radiographic evidence in the hands or wrists of articular erosions or osteopenia in or around the affected joints.

INITIAL EVALUATION

Patients with RA should be evaluated and treated by physicians who are familiar with the clinical management and treatment of the disease.

The initial evaluation of a patient with RA should include a clinical history and physical examination.

The **clinical history** should include background information that is important for RA diagnosis and treatment, including previous diseases, life style, gynecological history, and occupation. If the patient has been diagnosed with RA, the history should describe the clinical characteristics of the disease obtained by patient interview and by reviewing reports and other documents provided by the patient such as radiographs and laboratory tests. An understanding of how RA has evolved requires knowledge of all types of previous and concurrent treatments, especially with analgesics, NSAIDs, corticosteroids, and DMARDs, including the dosage, duration, reasons for withdrawal, tolerance, and side effects.

In the **physical examination,** note should be taken of the presence of pain, joint inflammation, deformities, and subcutaneous nodules.

The evaluation and monitoring of RA should be based on a systematic evaluation of a minimum set of parameters including joint pain and inflammation, the patient's global assessment of pain, global assessment of disease, functional disability, acute phase reactants, and radiologic evidence of damage.

Validated methods should be used to assess the number of painful joints and the number of

swollen joints. Although the clinician will consider different factors in the choice of which index to use, this guideline recommends the ACR count.

The articular indices assess the degree of pain and swelling by counting the number of painful joints and the number of swollen joints. Different methods have been described, varying in the number of joints evaluated, although only four are in widespread use: the ACR count, Ritchie index, 44-joint index, and 28-joint index.

ACR count. The ACR count is considered to be the most complete index and is the US standard. It includes an evaluation of tenderness in 68 joints and swelling in 66 joints (excluding both hips). The following joints are assessed: distal interphalangeal, proximal interphalangeal, metacarpophalangeal, wrist, elbow, shoulder, acromioclavicular, sternoclavicular, temporomandibular, hip (only for pain), knee, ankle, subtalar, metatarsophalangeal, and proximal interphalangeal joints.

The subjective experience of pain should be assessed by the patient. It is recommended that pain be measured using a horizontal visual analog scale, 10 cm in length, divided by vertical marks into ten equal 1-cm segments. The measurements should be accompanied by numeric descriptors from 0 to 10, with indicators at each end showing no pain (0) and worst pain (10).

A global assessment of disease should be made from the medical point of view and another one from the patient's point of view. For this measurement, the use of a 10 cm horizontal visual analog scale is recommended, with vertical marks dividing it into 10 equal 1-cm segments. The measurements should be accompanied by numeric descriptors from 0 to 10, indicating at each end "very good" (0) and "very poor" (10).

Global disease assessments by both the physician and the patient are useful because their evaluations may be quite different. The global assessment is very sensitive to clinical changes.

Self-perceived functional disability attributed to the disease should be evaluated using specific, previously validated questionnaires such as the Health Assessment Questionnaire (HAQ).

There are various ways to estimate functional capacity based on joint mobility or the ability to perform certain tasks as evaluated by an observer. The most widespread methods currently used consist of specific questionnaires for rheumatic disease such as the HAQ or its abbreviated form, the Modified Health Assessment Questionnaire (MHAQ), or the Arthritis Impact Measurement Scale (AIMS). They are based on the patient's own opinion about his or her disease. These questionnaires are standardized instruments of proven validity and reliability. They evaluate those health dimensions that are most affected by RA, particularly disability, especially in relation to physical function, and pain.

This guideline recommends the use of the HAQ, a 19-item self-administered questionnaire that evaluates self-perceived physical disability to perform different activities of daily living grouped into eight areas: dressing and grooming, rising, eating, walking, hygiene, reaching, gripping, and other activities.

Laboratory tests should include the acute phase reactants (APRs) erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). These two APRs are good indicators of the inflammatory activity of the disease.

Laboratory tests should consist of a complete blood count, acute phase reactants (ESR, CRP), rheumatoid factor (RF), liver function (GOT, GPT, GGT, alkaline phosphate, albumin), kidney function (creatinine), calcium, and urinalysis. The presence of hepatitis B and C virus should be evaluated (in relation to the hepatotoxicity of some of the drugs used in treatment).

These basic tests will facilitate RA monitoring and early detection of disease complications and side effects of treatment. Whether to include other, complementary tests is left to the judgment of the individual physician.

Radiographs of the hands, feet, and chest are recommended at the initial evaluation. Radiographs of the feet and hands should be repeated annually for the first 3 years of disease evolution, and thereafter as deemed appropriate.

The radiographs should be examined for the presence of bony erosions, which are more frequent at disease onset. About 70% of patients have erosions of the hands or feet by the end of the first 2 or 3 years. Their presence and the speed of onset are associated with poorer outcome. Radiographs of both hands and feet are justified by the fact that asymmetrical erosions (right or left) may appear, and by the observation that in the first 2-3 years of the disease, erosions appear only on the feet, without clinical symptoms, in up to 23-36% of patients.

A chest X-ray is recommended for initial evaluation and to identify the appearance of possible problems during the course of the disease and its treatment.

The use of a composite index of disease activity, summarizing various parameters in a single indicator, is a useful and valid procedure in assessing disease activity. As calculating such an index can be time consuming, this guideline leaves its use to the judgment of the individual rheumatologist. If one of these indices is used, however, this guideline recommends the Disease Activity Score (DAS), in any of its versions.

These indices differ in the number of parameters included as well as in the methods used for their calculation. Their advantages in comparison to conventional evaluation using single parameters are that they avoid duplicate measurements and are more sensitive to change. Their disadvantages are a certain degree of complexity in the calculations, difficulty of interpretation, and some problems related with how they are constructed.

The DAS includes the Ritchie index (see description in the guideline), the number of swollen joints out of 44 joints (NSJ44), ESR, and the patient’s global assessment of disease (PGA) on a visual analog scale (0 cm "very good" - 10 cm "very poor"). The DAS is calculated using the following formula:

$$DAS = 0.54 (\sqrt{RI}) + 0.065 (NSJ44) + 0.33 (In\ ESR) + 0.0072 (PGA)$$

There is a modified DAS based on counts of the number of painful joints (NPJ28) and the number of swollen joints (NSJ28) out of 28 joints:

$$DAS28 = 0.56 (\sqrt{NPJ28}) + 0.28 (\sqrt{NSJ28}) + 0.70 (In\ ESR) = + 0.014 (PGA)$$

The score for the complete DAS and the DAS28 can range from 0 to 10.

The initial and subsequent evaluation of patients with RA should include a continual estimate of disease prognosis.

The outcome of RA varies considerably among patients. Some treatment strategies, more aggressive and therefore more toxic, improve RA outcome when used early in patients with a high risk of developing functional disability or structural damage and/or of mortality. Since most radiographic changes and loss of functional capacity occur in the first few years of evolution, the earlier a disease prognosis is formulated, the earlier it will be possible to make an informed decision on the most appropriate treatment strategy.

RA outcome can be estimated more accurately by combining various factors than by considering a single factor. The factors predictive of serious disease (functional disability, radiologic erosions, and mortality) can be classified as sociodemographic, disease-dependent, and treatment-dependent. The sociodemographic factors associated with poor outcome are female sex and low educational level. Among the disease-dependent factors associated with poor outcome are positive RF, more than 20 swollen joints at disease onset, elevated CRP, ESR greater than 60 mm in the first hour, elevated HAQ at the first visit, early involvement of large joints, rapid appearance of erosions (≥2/year), and the presence of extra-articular manifestations (rheumatoid nodules, vasculitis, scleritis, or others). The treatment factors associated with better outcome are early initiation of DMARD treatment and total time in treatment with DMARDs during the course of the disease.

Factors related with the patient's psychological and social situation should be taken into account because they can affect the assessment of pain and development of disability.

Depression and anxiety are very frequent in RA from the time of disease onset due to the impact of confronting its diagnosis and evolution. Depression and anxiety are closely related with chronic pain and the development of disability. Some psychological characteristics of the patient (level of perceived helplessness, coping ability, level of self-management) play an important role as factors predictive of disability and health status. Patients who receive social support from family members, especially from spouses, have better outcomes and less disability.

A detailed evaluation should be made to rule out latent tuberculosis infection before beginning treatment with immunosuppresants, anti-TNF agents, or corticosteroids. If latent tuberculosis infection is present, prophylactic treatment with isoniazide is recommended.

CLASSIFYING RHEUMATOID ARTHRITIS

The classification of RA is based on the two characteristics that have the most influence on treatment decisions and outcome: the presence or absence of erosions and the number of swollen joints. This classification may be made more precise if other factors such as APR, HAQ, and RF are taken into account.

RA cannot be neatly classified into different categories. In this guideline, the classification of patients is based on two principles: first, classifying RA is useful for making treatment decisions and estimating patient outcome; second, the classification should help the physician in actual practice. In accordance with these two principles, RA is classified based on the two parameters that, in the panel's opinion, have the most influence on treatment decision and outcome: the presence of erosions and the number of swollen joints. The use of two categories for the presence of erosions (yes/no) and two categories

for the number of swollen joints (<6/≥6), gives four types of RA. Further differentiation in the classification process by considering other factors such as APRs, HAQ, and RF results in 144 different patient types, from the most mild clinical presentation (no erosions, <6 swollen joints, normal APRs, HAQ<1, and negative RF) to the most severe (erosions present, >10 swollen joints, elevated APRs, HAQ≥1, and high titers of positive RF). Each patient, according to the initial disease characteristics, should begin a specific treatment option (see chapter 4).

Two types of RA are excluded from this classification: "burnt-out" or end-stage RA and pseudopolymyalgic RA.

"**Burnt-out" or end-stage RA** is RA without inflammatory activity and with complete or practically complete destruction of the patient's joints. It is characterized clinically by joint pain at rest or with minimal exertion, joint deformities, severe muscular atrophy, extreme functional disability, and radiographic evidence of major joint destruction (erosions, subluxations, and ankylosis). The evaluation should rule out the presence of the extra-articular complications or manifestations of RA that most frequently appear at this stage of the disease, for example, skin ulcers, vasculitis, or amyloidosis.

Pseudopolymyalgic RA is a disease that affects patients over 60 years of age and is characterized by the sudden onset of symptoms, mainly affecting the proximal joints (shoulders and hips) as well as the knees and carpal joints. It is accompanied by considerable morning stiffness, negative RF, and a marked increase in APRs. Erosions do not usually develop and the prognosis is generally good, with possible spontaneous remission of the disease in 6-24 months.

The differential diagnosis of pseudopolymyalgic RA is difficult since it is very similar to polymyalgia rheumatica. It is usually managed effectively with corticosteroids. If a satisfactory response is not obtained, it should be treated the same as RA, taking special considerations into account for elderly patients.

MEDICAL TREATMENT OF RHEUMATOID ARTHRITIS

Initial treatment of rheumatoid arthritis

In general, patients with RA should be treated with a DMARD as soon as the disease is diagnosed.

At attempt may be made to treat only with NSAIDs and/or corticosteroids for a maximum of 3 months, and only in patients who have not used these drugs during the 3 months before the disease was diagnosed, who have fewer than 6 swollen joints, no erosions, negative RF, and normal APRs.

All RA patients who remain symptomatic (with pain and swelling) despite treatment with DMARDs should be treated with steroidal or nonsteroidal anti-inflammatory agents and analgesics.

Because of its efficacy and toxicity profile, methotrexate is the recommended initial treatment in all patients who have not previously received DMARD treatment. Nevertheless, initial treatment with other drugs is also considered acceptable, in accordance with the clinical classification of

disease shown in the accompanying table.

SIMPLIFIED CLINICAL CLASSIFICATION OF RA		Recommended treatment of first choice (in order of preference)
No erosions	<6 swollen joints	Methotrexate (1) Sulphasalazine (2) Chloroquine (3)
	≥6 swollen joints	Methotrexate (1) Injectable gold (4)
Erosions present	<6 swollen joints	Methotrexate (1)
	≥6 swollen joints	Methotrexate (1) Leflunomide (5) Methotrexate + injectable gold (6)

1. **Methotrexate** is more efficacious than oral gold (A1 evidence) or azathioprine (A2 evidence). No significant differences have been found in the efficacy of methotrexate compared with etanercept, leflunomide, sulphasalazine (A1 evidence), injectable gold (A2 evidence), cyclosporin, or infliximab (B evidence).
2. **Sulphasalazine** is more efficacious than hydroxychloroquine (A2 evidence), and no significant differences have been found in the efficacy of sulphasalazine compared with leflunomide, methotrexate (A1 evidence), oral or injectable gold, and D-penicillamine (B evidence).
3. **Chloroquine** is not significantly different in efficacy from cyclosporin, oral gold (A2 evidence), azathioprine, injectable gold, and D-penicillamine (B evidence).
4. **Injectable gold** is not significantly different in efficacy from oral gold (A1 evidence), cyclosporin and methotrexate (A2 evidence), or chloroquine, D-penicillamine and sulphasalazine (B evidence). It is less efficacious than azathioprine and cyclophosphamide (B evidence).
5. **Leflunomide** (A1 evidence) shows no differences in efficacy as compared to methotrexate and sulphasalazine (A1 evidence).
6. No clinical trials have evaluated the efficacy of treatment with **methotrexate+injectable gold** (C evidence).

Changes in treatment

Treatment failure or toxicity should be evaluated within a maximum of 3 months, and a change in treatment should be considered.

Whatever initial treatment is chosen, the patient should be closely monitored. If a satisfactory response is not obtained in 3 months or if serious drug-related toxicity develops, the treatment should be modified.

Changes in treatment due to toxicity or unsatisfactory response

If serious adverse effects appear, an alternative treatment should be substituted for the

treatment of first choice. If the treatment shows no toxicity but the response is unsatisfactory even after using the maximum dose, an alternative treatment should be substituted for the treatment of first choice.

For patients in whom alternative treatments fail due to unsatisfactory response, toxicity, or other reasons, the use of any DMARD or DMARD combination of proven efficacy is recommended (see tables 4, 5 and 8 of the guideline); if these fail, experimental treatments may be tried.

Changes in treatment due to toxicity or unsatisfactory response should be made in accordance with the following tables.

Alternative treatment in case of severe toxicity of initial treatment

SIMPLIFIED CLINICAL CLASSIFICATION OF RA		**First-choice treatment used**	**Alternative treatment in case of toxicity, in order of preference (supporting evidence)**
No erosions	<6 swollen joints	Methotrexate	Leflunomide (1) Injectable gold (2) Sulphasalazine (4)
		Sulphasalazine	Methotrexate (3) Injectable gold (2)
		Chloroquine	Methotrexate (3) Injectable gold (2)
	≥ 6 swollen joints	Methotrexate	Leflunomide (1) Injectable gold (2)
		Injectable gold	Methotrexate (3) Leflunomide (1)
Erosions present	<6 swollen joints	Methotrexate	Leflunomide (1) Injectable gold (2) Sulphasalazine (4)
	≥ 6 swollen joints	Methotrexate	Leflunomide (1) Injectable gold (2) Sulphasalazine (4)
		Leflunomide	Methotrexate (3) Anti-TNF (5)
		Methotrexate+injectable gold	Leflunomide (1) Anti-TNF (5)

1. **Leflunomide** (A1 evidence) shows no differences in efficacy as compared to methotrexate and sulphasalazine (A1 evidence).
2. **Injectable gold** has not been shown to have significant differences in efficacy as compared to

oral gold (A1 evidence), cyclosporin and methotrexate (A2 evidence), or chloroquine, D-penicillamine and sulphasalazine (B evidence). It is less efficacious than azathioprine and cyclophosphamide (B evidence).

3. **Methotrexate** is more efficacious than oral gold (A1 evidence) or azathioprine (A2 evidence). No significant differences in the efficacy of methotrexate have been found in comparison with etanercept, leflunomide, sulphasalazine (A1 evidence), injectable gold (A2 evidence), cyclosporin, or infliximab (B evidence).
4. **Sulphasalazine** is more efficacious than hydroxychloroquine (A2 evidence) and no significant differences have been found in the efficacy of sulphasalazine compared with leflunomide, methotrexate (A1 evidence), oral or injectable gold, and D-penicillamine (B evidence).
5. **Anti-TNF agents** (infliximab and etanercept) have been shown to be efficacious in the treatment of RA (A1 evidence), and they show no significant differences in efficacy with respect to methotrexate (B evidence for infliximab and A1 for etanercept).

Alternative treatment in case of unsatisfactory response to initial treatment

SIMPLIFIED CLINICAL CLASSIFICATION OF RA		**First-choice treatment used**	**Alternative treatment in case of unsatisfactory response, in order of preference (supporting evidence)**
No erosions	<6 swollen joints	Methotrexate	Leflunomide (1)
		Sulphasalazine	Methotrexate (2) Leflunomide (1)
		Chloroquine	Methotrexate (2) Leflunomide (1)
	≥ 6 swollen joints	Methotrexate	Leflunomide (1)
		Injectable gold	Methotrexate (2) Leflunomide (1)
Erosions present	<6 swollen joints	Methotrexate	Leflunomide (1)
	≥ 6 swollen joints	Methotrexate	Leflunomide (1) Anti-TNF agents (3) Methotrexate+anti-TNF (4) Methotrexate+chloroquine+sulphasalazine (5)
		Leflunomide	Methotrexate (2) Anti-TNF agents (3) Methotrexate+anti-TNF (4)
		Methotrexate+injectable gold	Leflunomide (1) Anti-TNF (3)

1. **Leflunomide** (A1 evidence) has not shown differences in efficacy compared with methotrexate and sulphasalazine (A1 evidence).

2. **Methotrexate** is more efficacious than oral gold (A1 evidence) or azathioprine (A2 evidence). No significant differences in efficacy have been found in methotrexate as compared to etanercept, leflunomide, sulphasalazine (A1 evidence), injectable gold (A2 evidence), cyclosporin, or infliximab (B evidence).
3. **Anti-TNF agents** (infliximab and etanercept) have been shown to be efficacious in the treatment of RA (A1 evidence) in comparison with placebo, and they show no significant differences in efficacy as compared to methotrexate (B evidence for infliximab and A1 for etanercept).
4. The combination of **methotrexate+anti-TNF agents** (infliximab or etanercept) has been shown to be more efficacious than methotrexate alone (B evidence).
5. The combination of **methotrexate+chloroquine+sulphasalazine** has been shown to be more efficacious than methotrexate alone or chloroquine+sulphasalazine (A2 evidence).

In addition to the panel's recommendations, there is scientific evidence regarding the efficacy of several drug combinations in case of failure of treatment with methotrexate or the antimalarials.

In case of failure with methotrexate, the following combinations have been shown to be more efficacious:

- Methotrexate+cyclosporin (A1 evidence)
- Methotrexate+chloroquine (A2 evidence)
- Methotrexate+azathioprine (B evidence)

In case of failure with the antimalarials, the following combinations have been shown to be more efficacious:

- Sulphasalazine+hydroxychloroquine (A2 evidence)
- Methotrexate+hydroxychloroquine (B evidence)

Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs)

The NSAIDs are used to modify the symptoms of RA. The use of NSAIDs is recommended at disease onset, when a new DMARD is introduced, and when uncontrolled isolated symptoms persist despite good response to a DMARD.

The use of NSAIDs is recommended in the following cases: 1) At disease onset, if it is low risk (<6 swollen joints, no erosions, negative RF, and normal APRs), they can be used alone or in combination with corticosteroids for no longer than 3 months; 2) when a new DMARD is introduced, NSAIDs can be used until the DMARD is capable of controlling the disease and its symptoms, generally from 2 to 12 weeks depending on the time needed for the DMARD to reach effective therapeutic levels; and 3) when uncontrolled symptoms persist (painful inflammation or swelling or morning stiffness) despite DMARD treatment, and there is no evidence of inflammatory activity that would justify raising the DMARD dosage or changing to a new treatment. The need for gastric protectors should be evaluated in each patient.

Treatment with corticosteroids

The use of oral corticosteroids at low doses is recommended in patients in whom NSAIDs are

not effective or are contraindicated for any reason. They can be used instead of NSAIDs or in association with them.

The corticosteroids should not replace treatment with DMARDs unless their possible role as a disease modifying agent should be shown. They are indicated as the treatment of choice only in the case of pseudopolymyalgic RA.

Corticosteroids should be used: 1) when NSAIDs are contraindicated or have a high risk of adverse effects (the elderly, associated morbidity); 2) as bridge therapy until the onset of DMARD action; 3) when NSAIDs do not effectively control inflammation (generally, by adding corticosteroids to the NSAID treatment); and 4) in the treatment of pseudopolymyalgic RA.

Treatment for pain

Analgesics are indicated to control pain. If there is no response, surgical treatment can be considered, especially to restore function and mobility.

Pain-control treatment should be instituted if pain persists despite the adoption of previous disease-control measures. Simple analgesics (e.g., paracetamol, ASA) should be used first. If pain persists, dipyridamole, NSAIDs, or codeine may be used.

If pain is due to neuropathy, tricyclic antidepressants (amitryptiline) and some anticonvulsants (gabapentine or carbamazepine) may be used. When pain is very localized, local analgesics such as capsaicin cream may be used.

Surgical treatment should be considered when pain does not respond to pharmacological treatments and is due to joint destruction, producing changes in the patient’s functional capacity. If pain is intense, there is no response to previous analgesic treatments, and surgery is not an option, opiate analgesics may be administered.

Special considerations in the treatment of elderly patients

Kidney and liver function should be monitored in elderly patients, and the dosage intervals of the drugs eliminated by these routes should be adapted accordingly.

The dosage of drugs eliminated by the renal route should be adjusted in elderly patients. This is because: 1) Even in the absence of kidney disease, renal clearance in elderly individuals is decreased by 35-50%, and 2) The elderly, and especially those who suffer RA, have reduced muscular mass, which produces a decline in the production of creatinine. Thus, an elderly individual may have a normal creatinine value even though creatinine clearance is altered.

Aging may also alter hepatic function, thus the metabolization of drugs that are broken down in the liver may also be reduced.

The possible appearance of adverse effects and drug interactions should be monitored in elderly patients.

In general, elderly patients have more than one disease and need treatment with multiple drugs. This, together with the higher frequency of adverse reactions in the elderly, means there is an increased probability of drug interactions and contributes to a larger number of side effects.

Special considerations in the treatment of rheumatoid arthritis during pregnancy

Women of childbearing age should be informed of the possible effects of RA and its treatment on pregnancy.

There is no evidence that RA has a negative effect on pregnancy outcome. The symptoms of RA disappear during pregnancy in 70% of cases, to reappear early in the postpartum period. Nevertheless, the disease commonly fluctuates and, at the very least, cycles of analgesics will be required.

The use of NSAIDs during pregnancy and breastfeeding should be avoided insofar as possible. Corticosteroids can be used under controlled conditions. DMARDs should be managed on an individual basis, and should preferably be continued during pregnancy.

NSAIDs should be avoided in the first and last trimester and during breastfeeding. If necessary, NSAIDs with a short half-life (ibuprofen or ketoprofen) should be used.

There is no evidence that the corticosteroids produce serious adverse effects at average doses during pregnancy, except for promoting glucose intolerance, fluid retention, and hypertension. Consequently, they should be administered under controlled conditions.

With regard to the use of DMARDs during pregnancy and breastfeeding, in the case of aggressive disease, the DMARD should be maintained at the minimum effective dosage, unless it has been shown to affect the embryo, fetus, or infant.

CRITERIA FOR RESPONSE TO TREATMENT

The objective of RA treatment is to induce complete disease remission or, alternatively, to achieve the best possible response.

RA patients who have spontaneous or drug-induced remissions in the course of their disease have a better medium-term outcome than those who have persistent clinical activity. However, the rates of complete remission with DMARDs and/or corticosteroids are low (18-25%) and are rarely prolonged. Complete disease remission, or at least attainment of the lowest possible level of inflammatory activity, is the only way to improve disease outcome.

Two basic approaches to defining clinical remission in RA have been described: the ACR criteria and the EULAR criteria.

ACR criteria for clinical remission

- Morning stiffness absent or not exceeding 15 minutes

- No fatigue
- No joint pain (by clinical history)
- No joint tenderness
- No soft tissue swelling in joints or tendon sheaths
- Normal erythrocyte sedimentation rate.

The presence of five or more of these criteria for at least 2 months is sufficient to classify a patient as in complete remission. Among the disadvantages of these criteria are the lack of guidelines on how to measure them, the fact that they are dichotomous, and that two of the criteria (fatigue and morning stiffness) are not included in the parameters recommended for the evaluation of RA patients.

EULAR criteria for clinical remission

The EULAR criteria use the DAS as a continuous variable of disease activity. A cut-off point below 1.6 on the DAS corresponds to the ACR definition of remission. Since the measurement scale is continuous, the cut-off point recommended by the EULAR may vary depending on future investigations.

Patients with RA should be clinically monitored for an indefinite period of time. Patients in complete disease remission should be seen every 6 months or 1 year, and patients with recent disease onset, frequent flare-ups, or persistent activity should be seen "on demand" (in general, every 1 or 2 months), depending on the treatment used and disease activity, until control is achieved.

To avoid an overload of patients, they can be seen in primary care during the periods between rheumatologist appointments to ensure clinical and laboratory monitoring and permit rapid referral to the specialist in case of disease reactivation and/or adverse effects.

Follow-up of patients with RA should be based on longitudinal monitoring of the parameters described in the initial evaluation: joint pain and inflammation, global pain assessment by the patient, global assessment of disease activity, functional disability, acute phase reactants, and radiologic damage.

One way to improve the quality of care for patients is to apply the treatment response criteria designed for use in clinical trials to daily clinical practice. Thus, it is proposed that the same parameters assessed at the initial evaluation be used to monitor patients and evaluate their response to treatment: pain and joint inflammation, global pain assessed by the patient, global disease activity assessed by the patient and by the physician, functional disability, and acute phase reactants. The same instruments used in the initial evaluation should be used in follow-up.

The physician’s subjective assessment of disease activity, although it is the most commonly used criterion in daily practice, is not recommended as the only criterion for response to treatment.

The treatment response criteria applied to individual patients should take into account: a) changes in disease activity and b) current level of activity. The clinician should evaluate the response to treatment, classifying it as satisfactory (complete remission of disease or sufficient even if not complete remission) or unsatisfactory (complete or almost complete lack of improvement). The evaluation can be made in accordance with any of the response criteria proposed in sections 5.4.1, 5.4.2, 5.4.3, and 5.4.4.

There is no published clinical experience in daily practice with any of the response indices developed for clinical trials. This guideline proposes the use of treatment response criteria based on two categories: **satisfactory response**, meaning complete remission of disease or a "sufficient" response, even though complete remission is not achieved, and **unsatisfactory response**, meaning complete or almost complete lack of improvement. The clinician can apply different response criteria to arrive at each of these categories. Two approaches that have been tested are described below: the ACR criteria for improvement and the EULAR definition of response. Other measures, such as the simplified Scott index and the Paulus criteria, are described in the guideline.

ACR response criteria

The ACR response criteria define a dichotomous result (response/no response) according to the following criteria:

- At least 20% improvement in the painful joint count and in the swollen joint count; and
- At least 20% improvement in at least three of the following parameters: ESR or APR, physician’s global assessment of disease activity, patient’s global assessment of disease activity, patient’s assessment of pain, and physical disability.

These criteria are known as the ACR20, reflecting the need for a 20% improvement in each parameter, which is considered the clinically relevant cut-off point. The fact that the criteria do not consider the current activity level limits its application in daily clinical practice unless it is adapted to take this factor into account. Thus it is proposed that these criteria be applied with the following modification:

- **Satisfactory response**: Meeting the following three criteria: 1) ACR20; 2) fewer than 6 swollen joints; and 3) no impairment of any joint producing intolerable loss of functional capacity in the opinion of the patient or physician.
- **Unsatisfactory response**: Not meeting the criteria for satisfactory response.

EULAR response criteria

The EULAR criteria use the disease activity scale (DAS), which takes into account both the degree of improvement and the patient’s current situation. It has been shown to be comparable in validity to the ACR response criteria in clinical trials. The definitions of satisfactory and unsatisfactory response, in accordance with the original DAS and DAS28, are shown in the accompanying tables.

EULAR DEFINITION OF RESPONSE (DAS)			
Current DAS	**DAS decrease**		
	>1.2	0.6-1.2	<0.6
<2.4	Satisfactory	Unsatisfactory	Unsatisfactory
2.4-3.7	Unsatisfactory	Unsatisfactory	Unsatisfactory
>3.7	Unsatisfactory	Unsatisfactory	Unsatisfactory

EULAR DEFINITION OF RESPONSE (DAS28)			
	DAS28 decrease		
Current DAS28	>1.2	0.6-1.2	<0.6
<3.2	Satisfactory	Unsatisfactory	Unsatisfactory
3.2-5.1	Unsatisfactory	Unsatisfactory	Unsatisfactory
>5.1	Unsatisfactory	Unsatisfactory	Unsatisfactory

SURGICAL TREATMENT

The rheumatologist should consider surgical treatment in any of the following situations: 1) when articular function does not improve or is notably worse; 2) when incapacitating pain persists; or 3) when there are potentially serious or limiting neurological complications.

The joint prosthesis is the most efficient surgical means to arrest progressive loss of functional capacity. Synovectomy may produce slight improvement in the synovectomized joints, but this effect is not maintained at 3 years. Arthrodesis is a good control measure but is more limited from the functional point of view.

Appropriate medical treatment will reduce the indications for surgery and will improve the likelihood of surgical success. Consultation with an orthopedic surgeon should not always be an indication for surgery, but the exchange of opinions and clinical evaluation will help improve the patient's clinical and functional status.

Before surgical intervention, an evaluation should be made of bone quality, the patient's motivation and preferences, an estimate of how surgery would change the course of the disease, and the extent to which it can reconstruct articular function and make the patient more independent.

REHABILITATIVE THERAPY

The objective of a rehabilitation program in RA patients is to improve pain, joint mobility, and performance of the activities of daily living. This is intended to prevent disability and maintain maximum personal independence. Rehabilitative techniques that can be used in treating RA patients are thermotherapy, physical exercise, prescription of splints, and occupational therapy.

Patients who undergo a rehabilitation program have 25 to 40% improvement in function.

LOCAL THERAPY

Local therapy in RA is indicated in joints with persistent disease activity despite adequate systemic control of the disease. The smaller the radiographic damage in a joint and the less systemic inflammatory activity of RA, the higher the probability that local treatment will have good results. Intra-articular infiltration with corticosteroids is the procedure of choice. Other

procedures are radioisotopic synoviolisis and chemical synoviolisis.

EXTRA-ARTICULAR COMPLICATIONS OF RHEUMATOID ARTHRITIS

Amyloidosis

Secondary amyloidosis should be suspected in RA patients who develop proteinuria, renal failure, gastrointestinal symptoms, myocardiopathy and/or hepatomegaly, and in those having elevated phase reactants concurrent with little clinical activity.

Anemia

Anemia in RA is usually asymptomatic, therefore periodic blood cell counts should be obtained including erythrocyte, leukocyte and platelet counts, calculation of the mean corpuscular volume (MCV), reticulocyte count, and general liver and kidney function tests.

Cardiological complications

Cardiac involvement should be suspected in the presence of pericardial-type pain, heart failure, or conduction abnormalities. The two most frequent complications are pericarditis and myocarditis.

Osteoporosis

Osteoporosis should be suspected in the presence of vertebral or peripheral fractures not due to trauma. When RA is first diagnosed, all patients should be evaluated for the main risk factors for fracture and loss of bone mass; this analysis should include both RA-associated and independent risk factors.

Pulmonary complications

The presence of pleuritic pain, dyspnea, or hemoptysis is suggestive of pulmonary disease in RA patients. Pulmonary complications may include pleural disease, rheumatoid nodules, interstitial fibrosis, or bronchiolitis obliterans with organizing pneumonia.

Felty’s syndrome

Felty’s syndrome is indicated by the presence of splenomegaly, leukopenia (< 3,500/mm^3), and neutropenia (<2,000/mm^3) in patients meeting RA criteria.

Secondary Sjögren’s syndrome

A patient with RA is considered to have secondary Sjögren’s syndrome (SSS) if there are signs and symptoms indicative of xerophthalmia and xerostomia.

Vasculitis

Rheumatoid vasculitis is understood to be a set of vascular processes (periungual splinter hemorrhages, palpable purpura, polyarteritis nodosa) with variable outcome and treatment.